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Primary Extramedullary Leukemia of the Prostate: Case Report and Review of the Literature

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We present the case of a 67-year-old male with primary extramedullary leukemia of the prostate gland, the first reported case in the literature to the best of our knowledge. His initial symptoms consisted of episodes of urinary retention. He underwent transurethral resection of the prostate, and a diagnosis of high-grade lymphoma was rendered. He then received a course of doxorubicin-based lymphoma chemotherapy regimen. However, based on a panel of immunocytochemical stains, a diagnosis of extramedullary leukemia or chloroma was confirmed. His bone-marrow examination at this point was normal. He underwent radiation therapy to the prostate with a total dose of 3960 cGy. Seven months after his initial presentation, he progressed to acute nonlymphocytic leukemia (ANLL), M2 by FAB classification. He was successfully treated with induction and consolidation chemotherapy with Ara-C and idarubicin, and was maintained in complete remission up to 19 months of follow-up. Eight other cases of prostatic leukemia reported in the literature are presented. Five cases occurred in association with ANLL, 2 cases as sites of ANLL relapse, and 1 case in association with myelodysplasia. The use of immunohistochemical stains has aided us in diagnosis of extramedullary leukemia. Surgery, radiation therapy, and chemotherapy play complementary roles in the treatment of prostatic extramedullary leukemia. © 1996 Wiley-Liss, Inc.

Key words: prostate neoplasms, acute leukemia, nonlymphocytic leukemia, leukemic infiltration

INTRODUCTION

Extramedullary leukemia (EML), also termed granulocytic sarcomas or chloromas, are uncommon tumors composed of neoplastic myeloblasts and myeloid precursors. Since its first description by Burns in 1811 [1] and its limited definition by Rappaport in 1966 [2] to include only tumorous masses, EML now includes all forms of leukemic cell infiltrates seen in association with acute nonlymphocytic leukemia (ANNL) [3–5], myeloproliferative disorders [4,5,6], and myelodysplastic syndromes [7]. Various clinical situations of EML have been described, including its association with the diagnosis of ANLL [3–5], as an isolated site of ANLL relapse [8,9], and as primary EML in the absence of a diagnosis of ANLL [8].

The incidence of EML is hard to establish, with one series reporting 3.1% in 478 patients with ANLL [5]. Moreover, primary EML is rare, with a recent excellent review by Byrd et al. [8] reporting only 154 cases worldwide. Traweek et al. [6] reported an occurrence of 10% among 28 EML cases presenting with primary EML, whereas Neiman et al. [4] reported 30% primary EML cases in their series of 50 EML patients. Primary EML has been described to occur in almost any organ and predominantly includes the skin, lymph nodes, spine, small intestines, orbit, bone, and breast [8]. Although primary EML has been reported to occur in the kidney [8], bladder [10], and testes [11], it has never been reported to occur in the prostate gland. We hereby report a case of primary extramedullary leukemia occurring in the pros-

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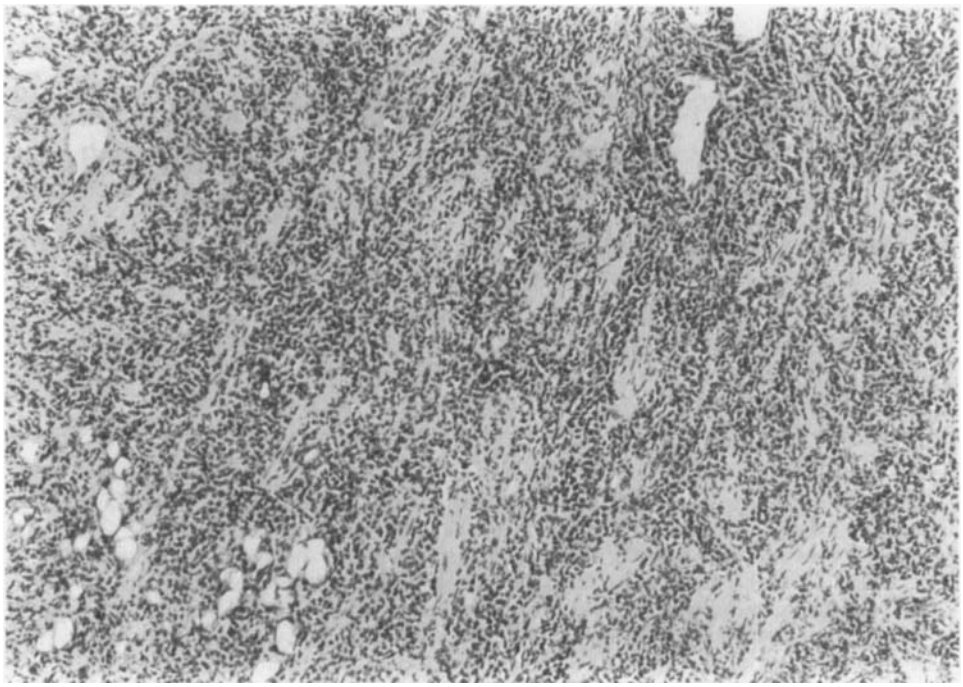

Fig. 1. Photomicrograph of prostate tissue (×25). Note diffuse leukemic cell infiltrate replacing prostate glandular structure.

tate gland followed by the occurrence of ANLL 7 months later. We will also review the other cases of prostatic chloromas reported in the literature.

CASE REPORT

A 67-year-old Caucasian male was admitted after repeated epidoses of urinary retention requiring catheterization. Rectal examination revealed prostatic enlargement. There was no lymphadenopathy or palpable enlargement of the liver and spleen. CBC revealed a white blood cell count (WBC) of 6.5 × 10^9/l, hemoglobin of 14.7 gm/dl, hematocrit of 45.3%, and platelet count of 354 × 10^9/l. A review of the peripheral blood smear was unremarkable. Prostate-specific antigen was 1.4 ng/ml. He subsequently underwent a transurethral resection of the prostate. An initial diagnosis of high-grade lymphoma was made. A full staging workup, including computerized tomography scans of the chest, abdomen, and pelvis, as well as bilateral bone-marrow aspirates and biopsies, were unremarkable. He then received one course of chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Further review and immunoperoxidase staining of the initial prostate pathology supported the diagnosis of granulocytic sarcoma or extramedullary leukemia. A repeat bone-marrow aspiration and biopsy revealed no evidence of leukemia. He subsequently underwent radiation therapy to the prostate, with a total dose of 3,960 cGy.

Seven months after his initial admission, CBC revealed WBC of 2.6 × 10^9/l, with an absolute neutrophil count of 650/mm^3 and presence of blasts, hemoglobin of 12.7 gm/dl, hematocrit of 37.2%, and platelet count of 191 × 10^9/l. Bone-marrow aspirate and biopsy were consistent with ANLL, M2 by FAB classification. The patient then received induction chemotherapy consisting of cytarabine arabinoside and idarubicin. He achieved complete remission and subsequently received two cycles of consolidation chemotherapy consisting of cytarabine arabinoside and idarubicin. The patient remains in complete remission, 19 months after the diagnosis of ANLL.

MATERIALS AND METHODS

The prostatic tissues and bone-marrow biopsies were fixed in 10% formalin, embedded in paraffin, and stained with hematoxylin and eosin. A panel of immunoperoxidase stains was performed on the prostatic tissues and included leukocyte common antigen, cytokeratin, lysozyme, myeloperoxidase, CD15, CD68, CD20, CD3, and CD45RO. The bone-marrow aspirate was analyzed by flow cytometry and the GTG banding method for chromosome analysis.

A MEDLINE search from 1964–1995 was done using the terms of chloroma, granulocytic sarcoma, extramedullary leukemia, leukemic infiltrate, prostate, prostate neoplasm, and prostate pathology. Bibliographies of literature

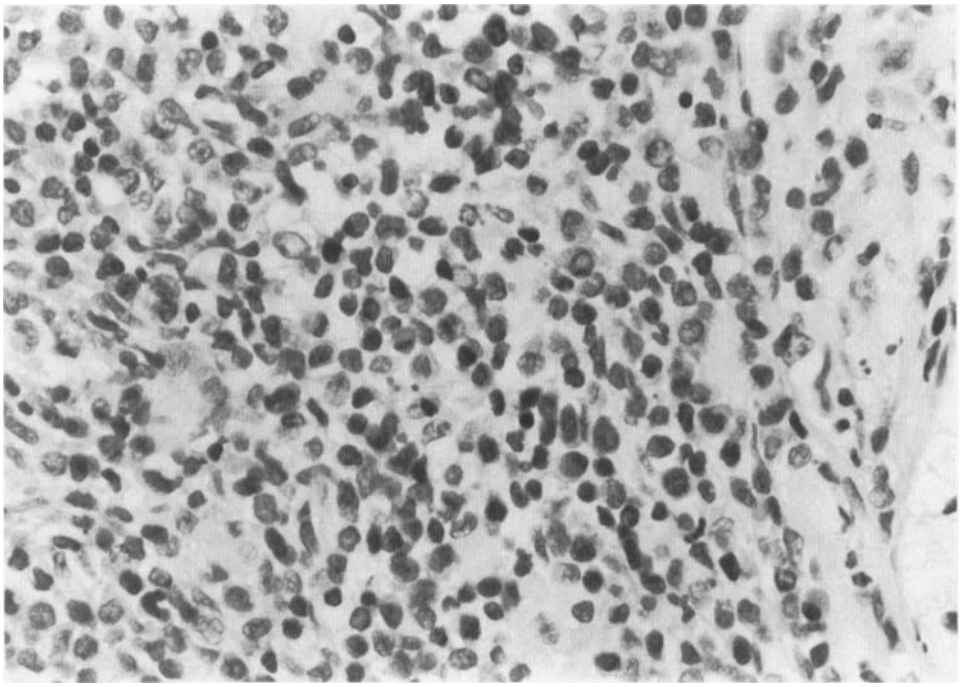

Fig. 2. Photomicrograph of prostate (×100). Note immature myeloid cells.

materials obtained from MEDLINE were likewise reviewed.

RESULTS

Microscopic examination of prostate chips revealed prostatic tissue extensively infiltrated with a monomorphous population of medium-sized cells with dispersed chromatin and scanty cytoplasm (Figs. 1, 2). The nuclei had irregular contours, and many were lobulated or folded. Nucleoli were inconspicuous or absent. The tumor cells were noted to have a high mitotic rate. Scattered eosinophils and eosinophilic precursors were admixed with the tumor cells. Tumor cells stained positive with leukocyte common antigen (LCA) and negative with cytokeratin. Further review and immunoperoxidase staining revealed the tumor cells to be positive for myeloperoxidase, CD68 (a lysozyme-associated antigen), and CD15, and negative for B-cell (CD20) and T-cell (CD3, CD45RO)-associated antigens. Many of the tumor cells were noted to express lysozyme; some of the immature cells were positive for chloroacetate esterase.

Peripheral blood smear revealed 28% blasts with high nuclear/cytoplasmic ratio. Auer rods were seen. The bone marrow was hypercellular, with left shift of granulopoiesis. Thirty percent blasts were noted, and these stained positive with myeloperoxidase. The majority of immature cells expressed CD33, HLA-DR, and CD34 antigens. Chromosomal analysis did not reveal any abnormalities.

The cases of extramedullary leukemia involving the prostate gland identified in the MEDLINE search are outlined in Table I. The mean age of these patients was 65 years. Five cases presented with known diagnoses of ANLL or with the presence of blasts in the bone marrow, 1 case with the diagnosis of myelodysplasia (refractory anemia with excess blasts), and 2 cases as sites of ANLL relapse. The present case is the first reported of primary EML of the prostate gland.

Most of these cases (8 out of 9) were symptomatic or had obstructive renal failure, prompting surgical intervention. The present case was initially misdiagnosed as lymphoma, as discussed later. Two of these cases were associated with ANLL, M2. Case 2 contained the translocation of AML1 gene in chromosome 21 and of ETO (for eight twenty-one) gene located in chromosome 8. Three cases, including our patient, were noted to have eosinophils and eosinophilic precursors in the prostate tissues.

DISCUSSION

Extramedullary leukemia of the prostate are rare tumors, with only 8 well-documented cases reported in the literature. The current case is the first reported occurrence of primary EML of the prostate gland, to the best of our knowledge.

Our case was initially misdiagnosed and, as such, treated as lymphoma. This is not surprising, since as high as 50% of all EML cases are initially diagnosed as lymphoma [4,8,10]. The presence of eosinophilic myelo-

TABLE I. Extramedullary Leukemia of the Prostate*

Case no. (Ref)	Age (years)	Symptoms	Diagnosis	Treatment	Outcome	Pathology
1 (5)	59	None	Acute nonlymphocytic leukemia (ANLL)	6-mercaptopurine	n/a	Diffuse leukemic infiltration of retrosternal, paravertebral, right atrium, and prostate gland
2 (9)	68	Obstructive renal failure	ANLL, M2 9 years earlier; sole site of ANLL relapse	TURP, chemotherapy: mitoxanthrone, Ara-C	CR of prostate after chemotherapy; bone marrow relapse (ANLL M2) 7 months later	Prostatic infiltration with immature cells expressing AML1/ETO gene rearrangement
3 (13)	79	Prostatism	None	TURP	Postoperative death	Diffuse leukemic infiltrate in kidney, prostate, liver, spleen, and bone marrow; eosinophilia in prostate noted
4 (14)	72	Urinary retention, hematuria	Myelodysplasia	TURP, radiation therapy: 2,100 rads	Resolution of symptoms	Leukemic infiltration in testes, prostate, and epididymis Eosinophilia in prostate noted
5 (14)	61	Urinary frequency, hematuria	ANLL	TURP, chemotherapy: doxorubicin, Ara-C, Vincristine, prednisone	Improved symptoms; not in remission after 3 induction therapy. Death 5.5 months after initial diagnosis	Leukemic infiltrate completely replacing prostate tissue
6 (15)	65	Urinary retention	None	None	Preoperative death	Diffuse leukemic infiltration in bone marrow, prostate, kidney, heart, lungs, spleen, and small intestines
7 (16)	59	Urinary retention	Acute myelomonocytic leukemia 19 months earlier	Suprapubic prostatectomy	Systemic and CNS relapse 1 month later	Leukemic infiltration of the prostate
8 (17)	56	Urinary retention	Subacute monocytic leukemia	Attempted TURP, suprapublic cystostomy	Death 64 days after diagnosis	Marked infiltration of prostate gland with immature monocytes
9 (present case)	67	Urinary retention	None	TURP, chemotherapy: CHOP radiotherapy to prostate bed	Development of ANLL 7 months later	See text

*TURP, transurethral resection of prostate; CHOP, cyclophosphamide, doxorubicin, vincistine, and prednisone; na, not available; CR, complete remission; CNS, central nervous system.

cytes and eosinophils, once considered a sine qua non for EML, would have suggested the diagnosis of EML [4]; however, this is nonspecific and may be present in other malignant processes [3]. The use of immunohistochemical stains like myeloperoxidase, CD68, CD43, and CD20 may identify up to 96% of EMLs in tissue paraffin sections [6].

Byrd et al. [8] identified 20 cases of primary EML treated initially with lymphoma chemotherapy regimens. They reported a median time of 12 months from initial diagnosis to development of ANLL, and a median time of 3 months from ANLL to death. This favorably compares to our patient, who had a 7-month interval from initial diagnosis to ANLL, and is currently disease-free 19 months after the diagnosis of ANLL. In another study, administration of chemotherapy in primary EML was associated with a lower incidence (41% vs. 71%) and longer delay (36 vs. 6 months) of subsequent leukemia development compared to local therapy alone. Prolonged survival was also noted among the patients who received any form of chemotherapy compared to local therapy alone [12].

Most cases of prostate EML were symptomatic, necessitating transurethral resection of the prostate [9,13,14], suprapubic prostatectomy [16], or cystostomy [17] to relieve urinary obstruction. It is hard to assess the potential benefit of adjunctive radiation therapy in cases of prostatic chloroma, including the present patient. In a series of 54 courses of radiotherapy given to 33 patients with symptomatic EML, 92% had significant clinical reduction of symptoms, and among these, 48% had objective complete responses [18]. There was a trend favoring higher radiation doses. This would indicate that these tumors are radioresponsive. However, median survival from EML to death in this series was only 7.1 months.

CONCLUSIONS

In summary, our clinical awareness of extramedullary leukemia and the use of immunohistochemical stains have improved our diagnostic accuracy in these rare neoplasms. Radiation therapy may be effective in symptomatic prostatic extramedullary leukemia. Systemic chemotherapy may improve the outcome in primary EML.

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